THE FAILING HEART

*Transcription of a Panel Meeting on Therapeutics**

CHARLES E. KOSSMANN . . . Moderator

Associate Professor of Medicine, New York University College of Medicine

Panel Members

ROBERT C. BATTERMAN

Assistant Professor of Medicine, New York Medical College

CARY EGGLESTON

Associate Professor of Clinical Medicine, Cornell University Medical College

LUDWIG EICHNA

Associate Professor of Medicine, New York University College of Medicine

CHARLES K. FRIEDBERG

Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University

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MODERATOR CHARLES E. KOSSMANN: Ladies and Gentlemen, it is my privilege to welcome you to this fifth of the monthly panel conferences on therapeutics arranged for you by The New York Academy of Medicine. As you know, today the subject is "The Failing Heart."

I need hardly say to this group of practicing physicians anything about the magnitude of this problem which I think you will agree is becoming greater as the population ages. It is also becoming greater because it appears that the man or woman with the failing heart lives a very much longer time than he or she formerly did. I think we can ascribe this to two important changes that have been made in the last decade or so in the management of the failing heart. I would say that those two important changes concern the advent of non-toxic mercurial diuretics and the use of the sodium restricted diet.

This panel is purely one on therapeutics. There will be an usher going up and down the aisles with paper for any of you who want to submit a question. The whole purpose of this panel is to answer your questions on the management of the failing heart. This panel has not met before this moment. We have no pre-arranged program. There will be no introductory remarks with two exceptions. First, I would like to take a few moments to introduce to you the members of your panel.

From the customary left to right, we have Dr. Cary Eggleston, Associate Professor of Clinical Medicine, Cornell University Medical College. I think all of you know Dr. Eggleston. Perhaps not all of you know that the first paper on digitalis dosage written by him was in 1915, a considerable period of time, perhaps, before most of us had even thought of entering medical school. He is the elder statesman of this panel and will keep the younger members in check in case they get a little wild.

The next man is Dr. Charles K. Friedberg, Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University. You all know Dr. Friedberg from the excellent book that has appeared in recent years under his authorship.

The next man is Dr. Robert C. Batterman, Assistant Professor of Medicine, New York Medical College. Dr. Batterman has devoted a great part of his professional life to the study of the mercurial diuretics and digitalis glycosides and he was also instrumental in introducing to clinical medicine a very important drug in the management of the patient with a failing heart, namely, meperidine hydrochloride (Demerol).

The last man is Dr. Ludwig Eichna, Associate Professor of Medicine,

New York University College of Medicine. Dr. Eichna is on the panel because of his interest in the hemodynamics of congestive heart failure. We shall call on Dr. Eichna for several aspects of management of the failing heart that may relate to its hemodynamics. Those are the first of the introductory remarks that I said would be made.

The second is this: I think that before we go into a discussion of the failing heart we ought to be pretty clear in our own minds what we mean by the failing heart. I think all of us have a pretty good general conception of what that is, but perhaps before we go into therapeutics, it would be well just for the record to be sure what we mean by the failing heart and so for a definition of the failing heart I am going to call on Dr. Eichna.

DR. LUDWIG EICHNA: My first comment is, oh, dear! I think the panel could easily get bogged down in a definition of the failing heart without any "ifs," "ands" or "buts" and with the realization of the tremendous assumptions made, suppose I give the following definition: The failing heart is one in which, for some as yet unknown reason, the chemical energy which is available to the myocardium is not properly transmitted into mechanical energy with the result that the myocardium cannot perform the work of propelling a sufficient amount of blood for the needs of the total bodily metabolism. As a consequence of this failure of blood supply in the required amount to all of the organs there results the commonly recognized syndrome of venous congestion, whether it be in back of the right ventricle to give congested veins, a large liver, edema or whether the venous congestion be back of the left ventricle to give dyspnea, orthopnea and rales. It is on these peripheral manifestations that we base our diagnosis of the more serious primary defect. This is the best I can do.

MODERATOR KOSSMANN: Thank you, Dr. Eichna.

Would you like to emphasize that there are some situations that could easily be confused with congestive heart failure?

DR. EICHNA: This, Dr. Kossmann, is a problem which is interesting us much at the moment. I mentioned that the failing myocardium gave rise to a series of peripheral manifestations and that on the basis of these peripheral manifestations we come to a conclusion as to what is wrong with the myocardium. Now if you will think for a moment, these peripheral manifestations are non-specific. They are simply the manifestations of venous congestion.

Just one example of where venous congestion may occur without a failing heart. If you have an anuric patient with lower nephron nephrosis and that patient is overloaded with intravenous fluids, the circulation becomes congested, he develops engorged neck veins and a large liver. He becomes edematous. Rales are present. He may develop pulmonary edema and he may die. This is not due, in my mind, to a failure of the heart. This is venous congestion induced artificially by overloading the circulation. This, Dr. Kossmann, I think is one type of venous congestion which is non-cardiac, which probably cannot be treated in the same manner as the same symptoms and syndrome developing from failure of the myocardium itself.

MODERATOR KOSSMANN: Thank you, Dr. Eichna.

I think perhaps that starts us off, at least in the right direction. *Now I would like to say I have a question here that is related, as a matter of fact, to this whole problem and it is: Can a normal heart be made to fail, for example, by prolonged, high rate tachycardia?*

Would you like to answer that, Dr. Eggleston?

DR. CARY EGGLESTON: Dr. Kossmann, I think probably a normal heart can be made to fail as a result of a prolonged high degree of tachycardia. On the other hand, one can retort to that opinion by pointing out that the tachycardia's occurrence is an indication of some disturbance in the heart or the heart's mechanism, and hence we may not be judging right to classify such a heart as a normal heart.

MODERATOR KOSSMANN: *Are there any other members of the panel who would like to comment on this particular problem?*

DR. ROBERT C. BATTERMAN: I think the question presented, whether a normal heart can develop heart failure as the result of a tachycardia, is one dependent upon time. The behavior of a normal heart that has been functioning well before it is given too much work to do as in the case of stress, whether it is a tachycardia from an irritable focus or tachycardia on the basis of excessive exertion, is dependent upon how long that stress is going to continue. As a rule in the normal individual with a short duration of that tachycardia, heart failure may not occur in the form we usually recognize as heart failure in terms of pulmonary edema, enlargement of the liver or peripheral edema. The patient may manifest dyspnea or a sense of suffocation but not real heart failure in the term of a complete break of the heart reserve. We all know that if a tachycardia should persist for many years, then as a compensatory mechanism for the tachy-

cardia the heart will hypertrophy and then at some time the patient will subsequently go into heart failure. In a normal individual a tachycardia of short duration will not result in heart failure.

MODERATOR KOSSMANN: Dr. Friedberg.

DR. CHARLES K. FRIEDBERG: I should like to make two comments about the discussion thus far. In the first place, I think it is important to emphasize that, as a rule, even with severe tachycardias, the normal heart does not fail, does not produce the series of symptoms that we call heart failure. In other words, it is valuable for differential diagnosis to distinguish between the heart which fails as the result of a tachycardia with a ventricular rate that exceeds 180 per minute and the heart, which, in spite of such tachycardia, does not fail. In short, then, the normal heart may begin to show symptoms of failure with tachycardia causing extreme strains, but this is the exception rather than the rule. This leads to the second point, namely, that many of the symptoms which we regard as heart failure are evidences of a load beyond the capacity of that heart, but even the normal heart has a reserve which though great is limited. Thus, for example, normally we can run a certain distance or we can walk a certain distance, or go up hill without dyspnea, usually a primary symptom of heart failure. That is true of the normal person. One can go so far but with a little more speed or a little more exertion even the normal individual has dyspnea. Yet we do not say he has heart failure at that moment. Similarly, but to a lesser extent, we can say that edema, as denoted by weight gain, can be induced if the normal person will take, for example, 25 grams of sodium chloride daily for more than three or four days. It is difficult to do but you could waterlog the patient and produce the clinical manifestations of heart failure. I don't think we can properly say that the patient had heart failure if he experienced dyspnea with unusual exertion or edema with enormous sodium intake. Therefore when we consider whether the normal heart can fail we really ought to say, does the normal heart fail with strains which are within the range of what we regard as normal activity?

DR. EGGLESTON: What would your answer to that question be if it were put to you?

DR. FRIEDBERG: You mean by a lawyer?

DR. EGGLESTON: By a medical man.

DR. FRIEDBERG: Yes or no, I would have to make the reply with a reservation. I agree with you that the normal heart may fail in the sense

that a patient having a marked tachycardia, which is especially persistent, begins to develop dyspnea and may develop rales at the bases of the lungs. I merely wanted to stress for the audience that it is more common that the normal heart tolerates tachycardia well, that the abnormal heart with a lesser reserve will more readily and more frequently develop the clinical syndrome that we call congestive heart failure.

MODERATOR KOSSMANN: While we are on the subject of tachycardias, I think everyone is aware that the patient with organic heart disease can develop tachycardia arising from a variety of foci. Let us assume that the patient has auricular tachycardia occurring in the course of some disease which might eventually go on to heart failure. *What would be the treatment of choice in the patient who has developed congestive heart failure as a result of auricular tachycardia, Dr. Batterman?*

DR. BATTERMAN: I think the choice of any therapeutic measure under such circumstances is dependent upon the underlying heart disease and not the tachycardia. If the patient has a myocardial infarction accompanied by auricular tachycardia, the choice of a certain drug might be quite different from the case where there was long-standing rheumatic heart disease and the occurrence of auricular tachycardia. But taking it as a group now, without knowing the etiology of the underlying heart disease, the drug of choice would be a digitalis preparation. Assuming that simple conservative measures such as carotid pressure, ocular pressure, induced vomiting, or sedation have not controlled the tachycardia, and the patient is in heart failure, then digitalization is indicated. Again we have to assume that the patient has not had any digitalis in the recent past or within a very reasonable period before the onset of the tachycardia.

MODERATOR KOSSMANN: *Dr. Batterman, is there any particular way you would prefer to give the digitalis in such a patient?*

DR. BATTERMAN: That again depends upon the severity of the signs and symptoms of the heart failure at the time the tachycardia is noted. If we are courageous enough not to treat a group of patients with a paroxysmal tachycardia, we note that the tachycardia sort of tires itself out the longer it persists and drugs which are less effective at the onset of the tachycardia are more effective later on. For example, if one were to use acetyl beta methyl choline, it is less effective immediately after the onset of the paroxysmal tachycardia than after the tachycardia has been present for several hours. If the patient is in serious, critical condition,

then the parenteral use of a glycoside is indicated. If the patient is in good condition, as you can judge from the clinical point of view—purely a rough guide—then oral digitalization would be preferable. The drug that I would try to avoid is quinidine because if quinidine does not work in these cases, then you may prevent the action of other therapeutic measures, because quinidine may be depressant on some of the pharmacologic actions of digitalis or acetyl beta methyl choline.

MODERATOR KOSSMANN: In myocardial infarction we occasionally see ventricular tachycardia. We also see ventricular tachycardia in the case of Stokes-Adams' seizures. There has recently been made available to the clinician a very potent and useful procaine amide, Pronestyl being the trade name. *Dr. Eichna, would you like to say something about the use of Pronestyl in the treatment of ventricular tachycardia, first in the course of myocardial infarction and second, in the case of complete heart block with Adams-Stokes' seizures?*

DR. EICHNA: The use of the drugs under the two conditions is entirely different. In a ventricular tachycardia with myocardial infarction there is every reason to attempt to suppress that tachycardia, the danger being of course ventricular flutter or ventricular fibrillation and death. Under such circumstances I would not hesitate to use Pronestyl, or if you wish, quinidine. I think experience has shown that ventricular tachycardia in the presence of complete A-V dissociation is an entirely different picture,—that here Pronestyl instead of preventing the tachycardia tends to potentiate it. Several papers in the literature during the past fall (1952) have indicated this and in our experience the same thing has occurred. Patients who have had ventricular tachycardia with Adams-Stokes' attacks on the basis of complete dissociation, and who were given even small doses of Pronestyl, have shown ventricular tachycardias, with in one instance an unfavorable outcome.

As to dose, I would give Pronestyl orally unless there is a specific reason to give it intravenously. If the patient with myocardial infarction is in shock, if it appears as though death is imminent, then I think, one might in spite of the lowered blood pressure give the drug intravenously at the rate of approximately 100 mg. per minute, not faster than 100 mg. per minute, to a total not to exceed one gram. If the patient can take the drug by mouth, I would give the same dosage by mouth because it is readily absorbed.

MODERATOR KOSSMANN: *Dr. Friedberg, sometimes in his enthusiasm*

the physician induces ventricular tachycardia with digitalis. What about the use of procaine amide in that situation?

DR. FRIEDBERG: I think the indication is just as good for procaine amide in ventricular tachycardia due to digitalis as in the type that Dr. Eichna discussed.

Of course, in all forms of therapy I like to attack the cause if that is possible. That means that one of the dangers, in cases of ventricular tachycardia due to digitalis intoxication, is the failure to recognize that the tachycardia is actually due to the digitalis and to misinterpret the tachycardia as an indication for further digitalization. Therefore the first point to stress is that one must recognize the etiology and discontinue the digitalis. Having done that one has three major drugs that may be used, and the one which I will give first choice is Pronestyl or procaine amide. Another is to consider the advisability of the administration of potassium salts since a diminution of myocardial potassium is concerned in the heightened irritability of the myocardium to digitalis. Finally, although there has been some difference of opinion about it, ventricular tachycardia due to digitalis may be controlled by quinidine. Such cases have been reported and I have observed this myself. There has been some hesitation by others to use quinidine in patients who have had ventricular tachycardia caused by digitalis.

MODERATOR KOSSMANN: Thank you, Dr. Friedberg.

Ladies and Gentlemen, your questions are lagging a little bit. The usher will come up and down the aisle; please give your questions to him. You are here to stump the experts by your questions, by your problems.

Dr. Eggleston, I have a question for you, a sort of general one, but perhaps it can start the ball rolling on digitalis. Which digitalis is the one of choice in the treatment of the failing heart?

DR. EGGLESTON: That, of course, is a matter of personal opinion and experience. My own experience leads me to give my first choice to crystalline digitoxin. I realize that that choice has certain drawbacks. It is not possible to induce digitalization where such is necessary with great rapidity by the administration of digitoxin, even when it is given intravenously. There is a certain lag period that we must allow to elapse. If the condition be sufficiently urgent then I would use one of the lanatosides. They act much more rapidly upon the heart than digitoxin, or I would use ouabain, the crystalline strophanthin G intravenously.

MODERATOR KOSSMANN: Whenever you get into a discussion of

which digitalis preparation is best for the treatment of the failing heart you are bound to have differences of opinion, so I think I am going to put this same question to all members of the panel. *Dr. Friedberg, would you like to say a word or two about what you consider the preparation of choice for the treatment of the failing heart?*

DR. FRIEDBERG: I often think of the digitalis preparations as I do of anesthetics, namely, that they are all useful. They can all be used and I prefer to use that with which I have acquired the greatest familiarity. Many of my patients who were originally digitalized by means of whole leaf are still continued on the whole leaf. On theoretical grounds, I think it is preferable today to use one of the digitalis glycosides and I think they will replace the whole leaf more and more because of certain advantages of standardization which I think will continue to improve. At the present time I use Digoxin, one of the lanatoside preparations, more frequently than any of the others in new patients. As I said, I think the leaf is still being used by most of my old patients. In addition I have been using gitalin, the one glycoside of digitalis purpurea not present in digitalis lanata. Digitoxin and gitoxin are two alkaloids present in both purpurea and lanata digitalis preparations. Gitalin is an interesting preparation because it is said that the range between the therapeutic and toxic doses is much greater than that of the other glycosides. I myself have always had a skepticism about such claims. But I find it an effective preparation and one which has not given me any difficulty.

MODERATOR KOSSMANN: *Dr. Friedberg, the man who made that claim is on your left and will be the next speaker.*

DR. BATTERMAN: The choice of a digitalis preparation is dependent upon many factors other than the glycosides or preparation itself. The problem is actually twofold, the initial digitalization and the maintenance of the restored compensated state. The initial digitalization is also dependent upon the emergency that arises and the rapidity with which you desire digitalization. For rapid digitalization you would prefer an intravenous or parenteral glycoside, preferably Lanatoside C. If you give it orally, then you must consider many factors. Again we go back to the type of heart disease that is present and whether or not that patient's heart has deteriorated to such a point that it has lost its ability to respond to a digitalis preparation. The use of the preparations of digitalis is similar to the use of any other drug in the field of medicine. There is no way of looking at the patient and predicting in advance what the opti-

mum dosage shall be. In a way you have to titrate your patient with decreasing doses taking into account the peak of level of each administered dose and the dissipation of effect of that particular dose. In other words, you cumulate a certain action depending upon the doses that you administer. You cannot predict what that optimum dose will be in advance, the point being that in the average patient you can achieve digitalization or a therapeutic effect before you achieve toxicity. If you want to consider averages, with most digitalis preparations, two-thirds of the toxic dose represent the therapeutic dose. We say the difference between the therapeutic dose and toxic dose is the therapeutic range but it is impossible to predict what that range will be in any particular patient. You may find that your patient will become toxic before a therapeutic effect has developed and the patient cannot respond to digitalization. That occurs in patients with myocardial infarcts or advanced fibrosis or patients with rheumatic heart disease that have advanced fibrosis. If you suspect that such a condition exists one would not use a preparation where the dissipation factor is prolonged. If toxicity should occur the toxic manifestations may persist for several days or weeks. You would prefer to use one that is rapidly dissipated like Digoxin. If, however, you take the average patient and the therapeutic range is only one-third, you have a better chance of obtaining the therapeutic dose without toxicity. It should be emphasized that no patient with heart failure should be treated to the point of toxicity. We would like to stop the repeated administration of the dose when the compensation occurs. In order to help you obtain a better range, we recommend gitalin, because the therapeutic dose is one-third of the toxic dose in the majority of the patients. That has a certain advantage in some of your patients, particularly in the ambulatory maintenance state. You may find that many patients cannot tolerate any equivalent dose of digitoxin, digitalis leaf or Digoxin. They become toxic without restoration of maintenance. They have abolished the therapeutic range. However, if you use gitalin in many of these patients you can now obtain a therapeutic effect because they will not become toxic with equivalent doses. For the usual patient we prefer gitalin, since it has a greater range. It does not persist in its toxicity as long as digitalis leaf, squill or digitoxin. However, in patients with advanced heart disease where you are afraid of irritability, then Digoxin is the drug of choice.

MODERATOR KOSSMANN: *Dr. Batterman, just for our information,*

would you tell us what the daily average maintenance dose of gitalin is?

DR. BATTERMAN: Half a milligram of gitalin is equivalent to one-tenth of a gram of leaf or one-tenth of a milligram of digitoxin, within certain biological variations. This may fluctuate plus or minus a quarter of a milligram, but that dose has the greatest predictability of producing maintenance and least likelihood of toxicity.

MODERATOR KOSSMANN: *Dr. Eichna, I wish you would continue this discussion along the line of this question: With purified glycosides readily available (and more expensive, I might say) does digitalis leaf still have a place in the treatment of the failing heart?*

DR. EICHNA: The answer is yes. To amplify, I think the problem should be considered from two points of view. Do you need digitalis in an emergency or do you have time and may you give a digitalis preparation more leisurely? Answering the second point first, do you have time, as far as I am concerned it is a toss-up whether you take digitalis leaf, Digoxin, digitoxin, gitalin or any of the other preparations. It seems to me that they all work about equally well. There is one proviso and I think Dr. Eggleston brought that out: Know your drug! If you have learned to know one preparation and how to use it, it will behave well for you. Of course, when you are faced with an emergency, then you are limited and most of the time I think that brings you down to Digoxin and ouabain. Ouabain is the fastest acting glycoside we have. It will produce its effect in about fifteen minutes. Digoxin will act almost as rapidly, in about thirty minutes. If you have a patient with rheumatic heart disease who is in labor and who has not been digitalized and is going into congestive failure or one who presents a surgical emergency, then these two preparations are very helpful. About a half milligram of ouabain should be given intravenously for an initial dose. If there is no effect, you may give another 0.2 mg. after half an hour. The dosage of Digoxin is usually from 0.5 to 1.0 mg. on the first dose. I recommend a half milligram rather than one, and repeat again after half an hour but do not give more than about 1.5 mg. within the first hour. In my own way of looking at it, if I get into trouble with any of the glycosides or the other preparations I almost always wipe the slate clean and go back to good old digitalis leaf until I get the patient straightened out. I must say that in spite of theoretical considerations and the gravimetric, instead of animal assay, digitalis leaf still has not failed.

As I have been a little bit against digitoxin because of the persistence

of toxic effects when they do occur, particularly the arrhythmias,—I would like to ask Dr. Eggleston what is your experience along that line?

DR. EGGLESTON: I am very glad you brought that up because I have been asked that same question on many occasions. I don't think that I have any particular difficulty with that problem. It seems to me that the dose for that agent in the majority of patients is pretty well established and if you do not exceed or fall too far below that dose you will obtain satisfactory digitalization in a reasonable period of time. That dose is somewhere in the neighborhood of 1.5 mg. for a patient. That is crystalline digitoxin.

As to the persistence of action, which may be and is considered by many to be a disadvantage, I do not see it that way. I think if we approach our therapeutic level of digitalization a bit cautiously toward the end of our administration we can avoid most of the toxic effects. I don't mean to say that that is applicable in all patients because it certainly is not. There are some patients who are supersensitive to all of the digitalis bodies, or particularly to some one or more of the entire range and one must then try out the different ones.

Years ago when we were investigating digitalis bodies, we found that they were mutually synergistic when introduced into the blood stream of the experimental animal. Fifty per cent of the toxic dose of any one plus 50 per cent of the toxic dose of any other equalled 100 per cent of the toxic dose of either of those preparations. I fail to see why we cannot therefore adjust our use of any of these digitalis preparations, glycosides, to meet the needs at hand and I have tried for many years to preach that upon every occasion, the problem is to meet the patient's needs under the existing conditions and I do not care whether you do that with one glycoside or another, or whether you do it with the whole leaf. The difficulty with the whole leaf is the amount of residual inactive material that is there and that cannot be estimated, plus the fact that the assay must be biological which we know is definitely less accurate than when we are attempting to use a dose based upon a crystalline preparation or a purified glycoside.

MODERATOR KOSSMANN: *Dr. Friedberg.*

DR. FRIEDBERG: I agree with everything Dr. Eggleston has said except I think that we should not infer from that that we are all able to handle the drug as well as he can. As a matter of practical experience I have found that since digitoxin has been available, the incidence of toxicity

has been, to my mind, appalling. I must assume, therefore, not that the drug cannot be given by the expert without this high degree of toxicity, but that there must be something in the drug or the dosage or our method of handling it at the present time which makes for a high incidence of toxicity and I think we ought to accept the fact as it is. I think one reason for it is that the original recommendation of the average of about 1.2 mg. for digitalization and 0.2 mg. daily for maintenance was faulty. This dosage may have been satisfactory for the digitalization, although I think for many people it was inadequate, but for maintenance I am sure it is much too high. In my experience most patients when digitalized can be managed perfectly well with 0.05 mg. daily, and a lesser number require 0.1 mg. and a still lesser number 0.2 mg. But most patients who take 0.2 mg. daily eventually develop toxicity which is very difficult to eliminate, as Dr. Eichna mentioned.

Since we are discussing the question of digitalization, intravenous and rapid, I should like to state that most of us hurry much too rapidly to digitalize the patient. The instances in which haste is necessary are very, very few. The instances in which some degree of urgency is valuable boil down to cases with auricular fibrillation and rapid ventricular rate. Those cases do not offer us a great problem in digitalization. On the other hand, patients with regular sinus rhythm who have congestive failure, need not be digitalized with great haste. In the first place, digitalis is rarely a dramatic drug in the treatment of cases with sinus rhythm, compared to other measures which we have. Secondly, it is in trying to digitalize such patients with regular sinus rhythm that we are apt to run into toxicity, in a futile effort to obtain a rapid, dramatic clinical improvement.

MODERATOR KOSSMANN: Ladies and Gentlemen, may I take just a moment to pull these remarks together for you? I think I may summarize them as follows: The addition of the glycosides to our therapeutic armamentarium in the management of the failing heart is a very real one, but one must not forget that even with the glycosides you still must do an animal assay except that the animal is your patient. Although it is of great advantage to have a preparation which has a fixed amount of active principle in it, nevertheless each patient requires an individual dosage and he must be, in a sense, biologically assayed with the drug. For the answer to the question, which preparation is the best, I think the gentlemen on the panel have made it clear that all of them have advantages, probably

all have certain disadvantages. For the practitioner it would appear wise to learn how to use one slow-acting preparation and one fast-acting preparation. Stick to those and you will find that your problems in the management of the failing heart will diminish, particularly the problem of getting the patient toxic, which seems to be the biggest difficulty when digitalis is used by the physician who is doing general practice.

Now, I have a whole handful of questions relating to digitalis and here is one that is rather important and touches on some of the remarks that Dr. Friedberg just made: Is it not a fact that patients with severe venous congestion sometimes do not respond to sufficient amounts of oral digitalis but do respond to parenteral digitalis? Would you like to discuss that, Dr. Friedberg?

DR. FRIEDBERG: I have not had that experience. I think it is a matter of time and dosage but where time is not an important element, I have not been able to find that parenteral digitalis will accomplish that which the oral will not.

MODERATOR KOSSMANN: *Dr. Batterman, would you like to say something?*

DR. BATTERMAN: I am in perfect accord with Dr. Friedberg. It is a question of time and dosage rather than one preparation having a superior effect upon the myocardium than the other. I think one thing has come out in the study of all the glycoside preparations. In terms of their action, —improvement of heart muscle efficiency,—whether you give them orally or by injection, they all act alike if equivalent dosages are used. It is a question of dose and not the speed of administration and not the glycoside that one uses.

MODERATOR KOSSMANN: *Dr. Eggleston, is bradycardia a contraindication to digitalis in the failing heart?*

DR. EGGLESTON: I think that depends upon the cause of the bradycardia or the type of bradycardia. If the bradycardia is due to a structural lesion in the bundle of His, so that when your patient is suffering from a complete A-V dissociation, it is no criterion at all. You don't need to use bradycardia as a measure for digitalization and those patients, if they are in congestive heart failure, can take the same digitalis dose as any other patient. Other bradycardias than that should be considered individually I believe.

MODERATOR KOSSMANN: *Along that same line, should digitalis be used in heart failure where there is complete heart block, with frequent*

Stokes-Adams' seizures?

DR. EGGLESTON: My answer to that would be, yes, you can use it.

MODERATOR KOSSMANN: *Is there any difference of opinion among the members of the panel?*

DR. FRIEDBERG: I don't think there is a real difference in my mind except that that type of case usually presents a much more acute problem with respect to the Stokes-Adams' syndrome. That problem is the measure which is the immediate indication for therapy. But if a patient in heart failure with an acute myocardial infarction had the Stokes-Adams' syndrome occurring frequently and if he were already on digitalis because of his heart failure, I would merely continue it and direct therapy to the control of the Stokes-Adams' attacks, that is with epinephrine.

MODERATOR KOSSMANN: *Dr. Eggleston, is digitalis of value in the patient with an enlarged heart without exertional dyspnea?*

DR. EGGLESTON: I think, Dr. Kossmann, that is a debatable point. It was thought by the Boston group of cardiologists that one might prevent further damage or further enlargement of the heart by the continued administration of digitalis in some one of its preparations. I don't think that there has been adequate evidence brought forth to support that contention. So I suppose I had better answer your question—no.

MODERATOR KOSSMANN: *Is there any difference of opinion among the members of the panel? Dr. Eichna?*

DR. EICHNA: May I make a comment on that? I agree completely with Dr. Eggleston and for what it is worth, the clinical investigator by measuring cardiac output has shown, and I refer now to Dr. Cournand and his group, that a large heart without congestive heart failure responds to digitalis in the same way as the normal heart, namely, a decrease in cardiac output rather than an increase in cardiac output, as is the case with congestive heart failure.

MODERATOR KOSSMANN: *Here is another question, which probably can be answered by Dr. Batterman: If moderately rapid digitalization is carried out orally with a shorter acting glycoside as Digoxin, how does one switch to digitalis leaf for further maintenance?*

DR. BATTERMAN: The assumption is you can get more rapid digitalization with one preparation orally than another and I think that is not exactly so. The rapidly acting glycosides only bring in the rapidity of action or the short latent period if you give them intravenously but if you give them orally, for clinical purposes, the speed of digitalization is

the same for all digitalis preparations. It takes anywhere from twelve to forty-eight hours, depending upon the dosage and the type of heart disease you have and you cannot obtain faster digitalization by using any particular preparation. But Dr. Kossmann's question brings up another fundamental fact and also emphasizes to some degree what Dr. Eggleston mentioned in terms of synergism. Any effect that you get from any one glycoside can be maintained by equivalent dosages of any other. If you should obtain complete digitalization with any preparation whether you obtain it by the parenteral or intravenous use, or orally, you can use any other preparation for maintenance in equivalent dosages. In other words, if you should have a patient who requires say 3.0 mg. of Digoxin for initial digitalization by the oral administration, the next day you can put that patient on 0.1 gm. of leaf and obtain the same effects as if you used a Digoxin dosage. Even though the Digoxin is rapidly dissipated from the body, the effects are not. The effects outlast the amount of the drug within the body.

MODERATOR KOSSMANN: *You have no further explanation for that, Dr. Batterman? It is confusing to many people how, with an excretory rate so much faster with the glycoside, you can maintain its action with a slower excreted preparation in equivalent dosage.*

DR. BATTERMAN: We have no explanation other than to point out that it is a very common experience in other pharmacologic actions of drugs that the action of a particular drug will outlast the amount of drug present within a cell or within an organ. I just have to bring to your attention the fact that if you give a local anesthetic for the treatment of neuritis, we know that procaine is very rapidly eliminated from the body and yet that painful state may be relieved as long as 24-48 hours. From a pharmacologic point of view, the action of the drug many times outlasts the presence of the drug within the body and the same thing holds true for digitalis preparations.

DR. EICHNA: It seems to me the problem is considerably different, Dr. Batterman. If you were to take a patient and digitalize him and then discontinued the medication, it might take you anywhere from weeks to months to find out what has happened to the patient before he reverts back into congestive heart failure. Therefore, the fact that you may go from one preparation to another preparation does not indicate that you have not actually allowed for excretion of the first dose and slowly built up with the second. It is not like a local anesthetic where the effect in

the skin is measured within the course of minutes. I agree that you can switch immediately from one drug to the other. I am not convinced of your explanation.

DR. BATTERMAN: May I continue?

MODERATOR KOSSMANN: Yes.

DR. BATTERMAN: Suppose you take a group of patients and digitalize them with digitalis leaf. If you should stop the use of digitalis at a point of toxicity and wait until that patient or group of patients returns to congestive failure, the average time is fourteen to sixteen days. That is the classic experiment for studying dissipation of effect because up to the time of radioactive digitoxin there has been no good chemical method of studying the amount of digitalis within the tissue. We study it in terms of returning congestive heart failure or return of tachycardia. If you take any such patient, if you know the rate of dissipation, say if he is going to go into failure on the fourteenth day, if you put such a patient on the maintenance dose a few days before, the patient will never go into failure even though you have completely eliminated the digitalis leaf as can be demonstrated by redigitalization at the end of a week. That patient can still maintain good cardiac reserve thereafter as long as the dissipation of effect has not been lost. In other words, if compensation is restored and that is what you are trying to do with any digitalis preparation, if that effect is not lost, a maintenance dose, which is nothing more than maintenance of compensation, will still continue to work.

Now let me give you another example because it has been quite confusing. In the days when ouabain or strophanthin was introduced there was considerable confusion as to how to put the patient on the maintenance dose of digitalis twenty-four hours later, because ouabain is very rapidly dissipated. As you know, if you did not give any more ouabain, four days later that patient or group of patients would be in congestive heart failure. Yet we know we can take that group of patients and give a full dose of ouabain or digitalis within twenty-four hours as though they had no ouabain previously.

It was thought that twenty-four hours after the initial digitalization with ouabain you had to start redigitalization. Actually it is not necessary, for as long as you have achieved compensation you can put that patient on a daily maintenance dose of any digitalis preparation and the patient will remain compensated and not lose that effect.

MODERATOR KOSSMANN: We have a lot of aspects of congestive

heart failure or the failing heart to consider from the therapeutic point of view. I am sorry we did not have time to answer all the questions on digitalis. *There is just one remaining question on digitalis that gives the practitioner a great deal of difficulty and I am going to ask Dr. Friedberg to answer it. If you have a heart that fails in the course of myocardial infarction, should you use digitalis?*

DR. FRIEDBERG: The answer would be yes, with this reservation that congestive failure needs some degree of definition. We define it in a rather broad sense. When acute myocardial infarction occurs there is a type of congestive failure in the sense that most patients with a severe infarction will have rales at the bases of the lungs and they may have some dyspnea. If this is defined as heart failure and if this is all there is, my tendency is not to use digitalis, because I regard this as merely a transient redistribution of the blood volume. However, if after several days, after the acute phase of shock and diminished cardiac output is passed, there is still evidence of congestive heart failure, as defined by symptomatology, then I use digitalis. I don't use it on the first day, not because I think it is dangerous, but because, as in many types of heart failure, the management of the causative factor is so much more important than the management of heart failure and I regard it as unwise to add another drug to those used in treating the infarction itself. For example, you know hyperthyroidism with heart failure is not really controlled unless you control the hyperthyroidism, etc., and so I wait a few days for readjustment of the myocardial infarction. Thereafter I give the drug if heart failure is present.

MODERATOR KOSSMANN: I would like to get into the mercurial diuretics a little bit because this, as I emphasized earlier in the hour, is probably one of the reasons why our patients with congestive heart failure stay around so long with us these days. *The first question I have here is: Can digitalis do anything for the failing heart which the mercurial diuretics cannot do? Dr. Eichna.*

DR. EICHNA: I don't have the answer. Perhaps to start the discussion I might simply describe several observations which we have been making. Patients are hospitalized with congestive heart failure. Hemodynamic determinations are made. The cardiac output is measured. The pressures behind the failing chambers are determined. The patient is then placed upon thiomerin, which we have chosen because it does not have the xanthine and we wish to get the diuretic effect alone. The patient has a

diuresis, loses weight, the venous congestion disappears, rales disappear and the liver gets smaller. A repeat study is done. Improvement in cardiac output is found. The pressure has returned to normal. If possible, the patient is exercised to determine his response to a work load. The patient is then digitalized with whatever preparation one may choose and when the patient has become toxic and then pulled back from toxicity, at least when we are sure he is fully digitalized, a third hemodynamic study is done. It is much too premature, Dr. Kossmann, but in about four or five patients so studied, we have found no hemodynamic difference between the second and third studies. This I realize is not an answer to your question. It does, however, raise an extremely pertinent point, namely, are we correct in our traditional concept that digitalis produces its effect by direct myocardial action. It will take long clinical observation on patients followed with diuretics alone to determine whether there is, or is not, a difference between patients treated solely with diuretics and patients treated with digitalis. This excludes patients who have arrhythmias because certainly if there is auricular fibrillation then digitalis is unquestionably the drug of choice.

MODERATOR KOSSMANN: Thank you, Dr. Eichna.

I think everyone is pretty much familiar with the clinically available mercurial diuretics but every once in a while there is a patient who does not respond to them or who becomes refractory. Dr. Batterman, what do we do when a patient becomes refractory to the mercurial diuretics?

DR. BATTERMAN: I would like to take it from a broader point of view, Dr. Kossmann, because in so doing, it is a little exception to what Dr. Eichna has stated. I have no argument with the dynamic observations.

DR. EICHNA: I simply stated an observation.

DR. BATTERMAN: I have no argument with the observations. I have observations from the clinical point of view. We were concerned with the effectiveness of diuretic agents and tried to determine from a practical point of view what could be the possible factor,—why patients have stopped responding to particular preparations when given in maximum dosage and given by various routes of administration. We found that heading the list was the fact that patients became refractory to mercurials if they were not on an optimum dose of a digitalis preparation. The heart is the central mechanism for heart failure and the so-called forward aspects produce a disturbance in kidney function so that you retain

sodium and therefore edema. If you haven't the central mechanism for maximum cardiac efficiency, the kidneys necessarily are not as effective. You can only obtain your maximum cardiac efficiency if you use the digitalis preparation adequately. In many of these patients adjustment of the dose of digitalis made the patient responsive to the mercurial. We have now been able to stop the mercurial because we have restored efficiency of the heart muscle.

I would like to point out this, when a patient goes into heart failure and there is a decreased efficiency of heart muscle, there is always some precipitating factor in such a patient. If you have removed the precipitating factor and restored the efficiency that existed prior to heart failure that heart should be as efficient as before. You can do that with digitalis. Under such circumstances the patient should no longer need any other therapeutic measure since you have restored normalcy. Many of these patients can now continue for many years on a daily dose of a digitalis preparation without needing any other therapeutic measure. It is when digitalis is less effective that other therapeutic measures are of help.

The second problem that arose in the use of mercurials was the question of exertion. Again this put an added load upon the heart so that the kidneys were less responsive. If we gave the mercurial diuretic to an ambulatory patient and had him walk around you could completely inhibit the diuresis whereas if the patient were at bed rest you will obtain a diuresis. The third factor is use of acidifying salts and I won't go into that at the moment because of time.

As to the presence of an excessive sodium restriction, if you haven't any sodium to be excreted you may not obtain diuresis. Other factors are low albumin or protein balance, and kidney function. We come back to the mercurial diuretic itself and its route of administration. If you give the maximum dose of a mercurial intramuscularly the best chance of getting a diuresis in a group of patients is no better than 60 per cent of your trials. In other words, 40 per cent of your patients will not respond, considering all factors which give you the maximum optimum result. If a patient does not respond to one mercurial intramuscularly, there is no point in trying another mercurial intramuscularly because you will get the same lack of response. You will either have to adjust the factors for lack of diuresis or use another parenteral route, giving it intravenously, which changes the amount of diuresis one obtains. It is also quicker. So, very often when the patient is refractory to the mer-

curial, it is because of the route of administration and the fact that there are other associated methods of treatment which are interfering with your diuresis. I omitted one other factor which is very commonly overlooked, chronic barbiturate administration. Phenobarbital or other sedatives which are commonly used in patients with heart failure will completely inhibit mercurial diuresis and if you decrease or stop the use of such preparations the patients may have a spontaneous response.

MODERATOR KOSSMANN: *Dr. Batterman, would you just say a word about the dangers of intravenous use of mercurials? There have been of course reports of death from the use of the preparation by this route. Also I recall, there have been several cases reported of death following the intramuscular route but there is a great reluctance of the physician in general practice to use the mercurials intravenously. Would you like to say a word about how he should give them if he must give them intravenously?*

DR. BATTERMAN: I think the history of the mercurial diuretics will give you the answer. The first mercurial diuretic was introduced in 1920, Novasurol, merbaphen. The first death due to its use was reported in the literature in 1925. That does not mean that death or reactions may not have occurred earlier but it did not hit the medical profession in terms of a report and so we have a five year "lag" period. This drug was used intravenously.

The next drug introduced, in 1924, was salyrgan, not with theophylline. The first death was reported in 1931, a seven year elapsed period. This drug also was used intravenously because it was very toxic by intramuscular injection.

The next drug introduced was novurit, mercuzanthin or Mercurophylline, in 1928. The first death for that was in 1933, five years later. That was also used intravenously. From 1940 to 1942 there was quite a furor about the occurrence of sudden deaths following the intravenous administration of the mercurials. Actually with the millions of injections that were used it was less than a fraction of a per cent, 40-50 such instances over a period of twenty years.

The next mercury diuretic introduced was mercuhydrin in 1945, and the intramuscular route was recommended as a safe procedure for this but the first death from mercuhydrin was reported in five years. This followed intramuscular administration.

The next was thiomerin in 1949, but because the basic chemical

structure of this is the same as mercurophylline, replacing the xanthine by a mercaptal group, you may obtain reactions to this if the patient has reactions to mercurophylline.

Now a new mercurial has been introduced, known as Cumertilin, and from the basis of past experience you can expect that within five years there will be a death or a reaction. It has to occur. The point I am trying to make is that deaths are dependent upon the basic chemical structure of all these products and you have to build up a sufficient number of patients over many years of use before you may obtain reactions or toxicity and it is immaterial which route of administration you use. If your patient has a reaction, then you should turn to another mercurial diuretic and not to a change in the route of administration.

MODERATOR KOSSMANN: Thank you, Dr. Batterman. Time is running out faster than I expected it would. *There are many aspects of the problem that we have not covered, so I am going to ask just one more question on the mercurials and then go on to one or two other aspects of the management of the failing heart. It concerns the oral mercurials. I am sure you have all been receiving in your mail numerous advertisements regarding the use of the oral mercurials. Would you say a word about that, Dr. Batterman? Do the oral mercurial diuretics have a place in the management of the failing heart?*

DR. BATTERMAN: Yes, only in the sense that they are used for maintenance, not for replacement of the parenteral injections. They cannot be used in the same conditions where one desires a rapidly dehydrating action in the patient. They cannot give you the same degree of diuresis, the same predictability of diuresis, no matter what dose you use by oral administration but if a patient accumulates edema rapidly and requires a parenteral injection twice a week or three times a week, then a daily dose of an oral preparation will decrease the accumulation of the edema to the point where one can decrease the number of injections. One should use rest periods in the sense that the patient should be given a few days of cessation of the use of the orally administered preparations every three weeks. The dose is one or two tablets every day, never to exceed that, because you will not achieve any greater diuresis with more. It takes several weeks before you achieve the effect you are looking for, the slow prevention of accumulation of edema.

DR. FRIEDBERG: You regard all the mercurials, that is, the oral ones, as being equal when you mentioned dosage?

DR. BATTERMAN: Equal in the sense of what one would obtain from accumulation but not toxicity. There are some more toxic than others. Neohydrin is, in my experience, the most toxic, having the greatest incidence of gastrointestinal irritation. Next is salyrgan-theophylline, Mercurophylline and the least toxic of all is the latest one, Cumertilin.

MODERATOR KOSSMANN: *I think we have to leave this very interesting aspect of the management of this syndrome to go on to three other aspects I would like the Panel to cover with you in the few minutes left. One is in relation to the electrolyte disturbances which occur with the failing heart and which will plague the physician, particularly in the terminal phases of the disease but which may occur at any time in the course of the disease, particularly if diuretic therapy is overenthusiastic. I have this question: May intractable heart failure be due to electrolyte disturbances and how should it be treated?*

Will you handle that, Dr. Friedberg?

DR. FRIEDBERG: The answer to this question of necessity must be given with reservations. We are making statements about electrolyte disturbances which I think will require revision. In general we say that if the mercurials are given very frequently and if at the same time the patient's sodium intake is low he may develop disturbances in the blood electrolyte pattern. These disturbances may be of two major types. In the first, the sodium is not substantially altered in its concentration from the level of about 140 mEq. per liter, but the chlorides are substantially below the normal of 103 or thereabouts, in other words, a chloride level below 90 or 80 mEq. per liter. At the same time there is usually also an alkalosis, as has been noted by elevation in bicarbonate, and frequently also a diminution in potassium. In such patients who develop what we call a hypochloremic alkalosis, with hypokalemia, the response to treatment is often very poor. Correction of the electrolyte pattern by the administration of ammonium chloride, preferably by mouth, supplemented by potassium if indicated by the low serum potassium concentration may result in a favorable clinical response. I should like to emphasize, both with respect to this and the next aberration in electrolytes, that one is often hard pressed to determine to what extent the clinical picture is the result of the electrolyte disturbance or whether these electrolyte disturbances do not develop more readily because we are dealing with a patient with such advanced heart failure that it is refractory to treatment.

The second abnormal electrolyte pattern is one in which both serum sodium and chloride concentrations are low and usually there is a mild acidosis associated with it. This is the so-called low-sodium syndrome. It is not necessarily due to depletion in the sense that much sodium is lost by diuresis. Many of these patients who are on low sodium intake virtually excrete no sodium in the urine. But they are taking fluids ad lib and so we have a dilution of the serum sodium, since the sodium excreted is not being replaced because the sodium intake is so low. These patients develop a very serious syndrome characterized by many clinical features, including nausea, apathy, or even stupor. They may go into shock. They may develop azotemia and they look as if they are moribund. Theoretically the indication is for hypertonic sodium chloride in an effort to correct the deficient electrolytes. Sometimes there is a temporary improvement. But a strikingly favorable result is infrequent because the low sodium syndrome is only partly due to the low sodium intake and the vigorous mercurial therapy but more especially is due to the patient's very poor cardiac state. That may be because the myocardium has reached an irreversible degree of heart failure. But it is often due to the fact that some of the therapeutic measures, a few of which were listed, were not properly carried out. In other words, if I might add one word to the treatment of refractory heart failure, it is to be sure first that you have eliminated all the contributory causes such as hyperthyroidism, etc., and other basic contributory diseases, and secondly that each of the measures utilized in the treatment of heart failure, rest, digitalization, sodium restriction, etc., has really been carried out as meticulously as you think it should be. In the average patient with heart failure, you can get away with a good deal, even though some of the measures are not perfectly executed but when you come to a patient who is very seriously ill with heart failure, any imperfection, whether over- or under-digitalization, over- or under-mercurialization, etc., will result in refractoriness and in these electrolyte disturbances.

MODERATOR KOSSMANN: Thank you, Dr. Friedberg.

A few weeks ago at one of the Cornell Conferences there was a discussion about the cation exchange resins. In that conference I understand that Dr. Eggleston made a statement that he could not get his patients to take "that clay." You see he is a little bit biased, but I am going to ask him a question. Dr. Eggleston, what part do you think the cation exchange resins play in the management of the failing heart?

DR. EGGLESTON: Dr. Kossmann, in my practice very little. The same statement that I made at the Cornell Conference holds today. I find it very difficult to get the patient to take with any degree of regularity enough of the cation exchange resins to accomplish any useful purpose and since those patients are already having a great many troubles, some of which are greater than their inability to take the cation exchange resin, I don't try to force them. I hope that the chemists will soon provide us with something more readily consumed by the patient.

MODERATOR KOSSMANN: *Is there any other opinion of the panel?*

DR. FRIEDBERG: Yes, I would like to venture an opinion. I find that in the type of patient that we see in the hospital (and that may not be representative because the patient is usually sent in because he is very refractory to treatment), in whom a really low sodium intake is essential for therapy, the use of the cation resin is extremely important and extremely valuable. I agree with Dr. Eggleston that clay is a very generous description of both the appearance and taste of the resins, but I believe that some of the newer preparations, even though they go by the same name, are more palatable and much more manageable and I feel that when the patient is sick enough, it is a very useful adjunct to other therapeutic measures. That does not mean that it is a routine necessity in the vast majority of patients with heart failure, just as it is not a routine necessity to limit sodium intake to 200 mg. a day in the average patient with heart failure who will do well with only moderate restriction.

MODERATOR KOSSMANN: *Just one last question—I think everyone will agree that even though oxygen makes up 20 per cent of the atmosphere, it is rather expensive when you get it in a hospital for a patient, and as I understand from Dr. Eichna, the patient with congestive heart very rarely shows an arterial oxygen saturation that is much below normal. In view of this apparent paradox is there a need for oxygen in the treatment of the failing heart, Dr. Eichna?*

DR. EICHNA: Very briefly, only in the severely ill patient. Remember that if you increase the oxygen concentration in the inhaled air, some of that oxygen will go into solution in the plasma in addition to being carried by the hemoglobin. That oxygen dissolved in plasma is available and will be made available to the tissues and consequently will permit a better oxygen transport to the tissues in the face of the lowest cardiac output that these patients have.

MODERATOR KOSSMANN: *Are there any other remarks from the panel?*

DR. BATTERMAN: I would like to mention another action of oxygen which is sometimes overlooked and that is it has a sedative effect. Patients in heart failure that have apprehension and have marked anxiety can be quieted by the use of oxygen. It is also an analgesic in a sense that the patients have less pain in the chest, less difficulty in breathing in using the accessory muscles. So even though you may decrease the dyspnea, and it may not be reflected in the change in oxygen saturation, from a therapeutic point of view these patients have subjective improvement.

DR. EICHNA: I would like to disagree with Dr. Batterman again. Oxygen does not have a sedative effect, Dr. Batterman. What it does do is to combat the cerebral hypoxia which is the factor which causes the patients to be restless. You see I mentioned that the oxygen in solution is available and it is available to the brain in these instances and it will frequently give the brain enough oxygen with its poor blood supply in order that the patient no longer has the disorientation, the restlessness and so on. I agree with you thoroughly with regard to the result in the therapeusis again, but I disagree with the explanation. Frequently the patients will do better if you put them in the oxygen tent as you say, rather than give them a barbiturate which will make them worse.

DR. BATTERMAN: I have no argument with the method of action with which I agree with Dr. Eichna. I am saying in terms of general value we see a sedative action which Dr. Eichna indicates.

MODERATOR KOSSMANN: Ladies and Gentlemen, the time is up. I must thank you for your enthusiastic participation in this panel and I regret that we were not able to answer all of your questions because of the lack of time. I also would like to take this opportunity on behalf of the Academy of Medicine to thank the members of the panel for giving us their expert opinions this afternoon.